Topic 2 – Antiagregation and anticoagulation – B

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0203

Analysis of antithrombotic therapy in patients over 75 years with non-valvular atrial fibrillation: do we apply the guidelines to elderly subjects?

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Introduction and Objectives: Atrial fibrillation (AF) is associated with a five times higher risk of stroke mortality. The benefit of anticoagulants in this context is widely recognized, particularly for older patients. Past studies show reluctance to anticoagulate seniors because of their bleeding risk. The European guidelines are regularly updated to promote the prescription of anticoagulants in this population. The purpose of this study is to evaluate the type and rate of antithrombotic prescription in real life in patients over 75 years with a history of non-valvular AF.

Methods: This is a retrospective study performed in Nimes University Hospital and Béziers Hospital. We studied 293 consecutive outpatients who consulted their cardiologist between April and November 2012. The following data were analyzed: CHA_2DS_2VASc score, HAS-BLED score, antithrombotic therapy, type of AF, demographics.

Results: The mean age of patients is 82 years (+/-5.1 years, 75-99 years). 219 patients (74.7%) receive oral anticoagulants: 60.4% are treated with vitamin K antagonists (VKA) and 14.3% with novel oral anticoagulants (NOACs). 60 patients (20.6%) get aspirin or clopidogrel alone or in various combinations, 14 patients (4.7%) receive no antithrombotic treatment. The rate of anticoagulation (VKA or NOACs) decrease moderately with age: 81.5% (75-79 years), 75% (80-84 years) and 67% after 85 years. It is more important in case of permanent AF (83%) versus paroxysmal (67%). Women are less anticoagulated (67%) than men (82%).

Conclusions: A higher rate of anticoagulation is found in this elderly population compared with previous "real life" records. Anticoagulant therapy is however less systematic in paroxysmal AF and women.

0382

AMPKalpha1 regulates actin polymerization, lamellipodia formation and clot retraction, in thrombin-stimulated platelets

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Background: Platelet activation requires sweeping morphological changes, supported by contraction and remodelling of platelet actin cytoskeleton. In epithelial and endothelial cells, AMP-activated protein kinase (AMPK) controls actin cytoskeleton organization through the phorphorylation of cytoskeletal targets, namely myosin regulatory light chains (MLC), cofilin and the vasodilator-stimulated phosphoprotein (VASP), extending the role of AMPK beyond metabolism.

Objectives: in this study, we hypothesized that AMPK was activated in thrombin-stimulated platelets and played a role in platelet secretion, aggregation and clot retraction, by regulating polymerization and/or organization of actin cytoskeleton through the phosphorylation of MLC, cofilin and VASP.

Results: Human platelets expressed exclusively the AMPKalpha1 isoform. In human purified platelets, thrombin led to a transient activation of AMPKalpha1 and to phosphorylation of its *bona fide* substrate, acetyl coA carboxylase (ACC). Platelets isolated from mice lacking AMPKalpha1 exhibited reduced aggregation and secretion response to thrombin, associated with a defect in ACC, MLC, cofilin and VASP phosphorylation. These changes were associated with an abrogration of thrombin-dependent F-actin formation. Moreover, the percentage of platelets able to form lamellipodia after immobilization on fibrinogen-coated coverslips and stimulation by thrombin, was significantly reduced in the absence of AMPKalpha1, indicating an altered cytoskeleton reorganization during spreading. More importantly, clot retraction was slower and less effective in KO platelets.

Conclusions: AMPKalpha1 plays a critical role in platelet function in response to thrombin through the phrophorylation of cytoskeletal targets and the subsequent regulation of cytoskeleton organization-dependent processes.

0361

Impaired P2Y12 inhibition by clopidogrel in patients with kidney transplantation

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Introduction: Several studies have indicated that impaired GFR is an important predictor factor associated with impaired platelet inhibition by clopidogrel. In chronic kidney disease, the presence of low platelet inhibition by clopidogrel is associated with adverse outcome following PCI and stenting. In the present study, we sought to determine if renal transplantation per se alters clopidogrel pharmacodynamics.

Patients and methods: 36 patients with kidney transplantation were enrolled in one single center (Nephrology Department, Hôpitaux Universitaires de Strasbourg). Control patients were 126 patients with different degrees of chronic renal failure, tested in the same conditions. Inclusion criteria were patients under clopidogrel treatment of 75mg per day for at least 8 days. Unstable patients or those presenting with any conditions that could account for reduced platelet inhibition by clopidogrel (heart failure, shock) were excluded. Treatment and medical history were collected at inclusion. Clopidogrel pharmacodynamics was studied using the VASP assay.

Results: Patients with kidney transplantation were younger (58.3 vs 72.6 years, $p<0.001$), less likely diabetics (39% vs 57%, p=0.12), presented a lower BMI (25.2 sv 27.2 p=0,05), the estimated glomerular filtration rate with the MDRD formula is better (47.9 vs 39.5ml/mn/1.73m2, p=0.15), and there is less inflammation. 89% patients in the transplantation group were under anti-calcineurin and 50% under steroids at low dose. Platelet reactivity Index a marker of the extent of P2Y12 inhibition was significantly higher in the transplantation group vs controls (60.1% vs 51.2% p=0.014). By multivariate analysis, high BMI and kidney transplantation were important predictors of residual platelet reactivity under clopidogrel treatment. After adjustment on eGFR with the MDRD formula, kidney transplantation remains an important predictor of alter P2Y12 inhibition.

Conclusion: In kidney transplantation patients treated by clopidogrel, impaired platelet inhibition exist, even after adjustment on estimated glomerular filtration rate. The mechanisms by which immunosuppressive treatments may alter clopidogrel pharmacodynamics requires further investigation

0136

Increased intracardiac VEGF and VWF levels revealed low grade inflammatory process and progressive endothelial damage in patients with AF

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Aims: Endothelial dysfunction seems to play a pivotal role in atrial fibrillation (AF). The purpose of this study was to investigate the relationship between AF and vascular endothelial growth factor (VEGF) and to investigate